## REMARKS

Claims 27 and 38-86 were pending in the instant application. Upon entry of the present Amendment, claims 27 and 38-86 are pending and presented for reconsideration. Applicants respectfully submit that no new matter is introduced by the present Amendment.

In a Response to Restriction Requirement earlier filed on March 22, 2006, Applicants elected Group I, drawn to claims 27, 38-59, 79, and 81, without traverse. Applicants further elected the species of Type II diabetes, for search purposes only. It is the Applicants' understanding that under 35 U.S.C. §121, an election of a single species for prosecution on the merits is required, to which the claims will be restricted if no generic claim is finally held allowable. Applicants further understand that upon the allowance of a generic claim, they will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R.§1.141 *et seq.*

Amendment and/or cancellation of the claims is not to be construed as acquiescence to any of the objections/rejections set forth in the instant Office Action or any previous Office Action of the parent application, and was done solely to expedite prosecution of the application. Applicants submit that claims were not added or amended during the prosecution of the instant application for reasons related to patentability. Applicants reserve the right to pursue the claims, as originally filed, or similar claims in this or one or more subsequent patent applications.

### *Acknowledgment of the Examiner's Withdrawal of Certain Rejections*

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection of claims 27, 38-59, 79 and 81-85 under 35 U.S.C. 112, first paragraph, as set forth in the Office Action dated February 22, 2007 and the Advisory Action dated August 7, 2007.

***Claim Rejections - 35 U.S.C. §103***

*Rejection of claims 27, 38-48, 50, 51, 56-59, 79, and 81-86 under 35 U.S.C. § 103(a)*

The Examiner has rejected claims 27, 38-48, 50, 51, 56-59, 79, and 81-86 as being unpatentable over Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) in view of Clancy *et al.* (US 20030087259) and Paquereau *et al.* (Anal. Biochem., 204(1):147-151, 1992). The Examiner states on pages 3-4 of the Office Action that, "Al-Hasani taught methods of studying genes related to glucose transport. Specifically, Al-Hasani investigated the relationship between the GTPase dynamin and endocytosis of the GLUT4 glucose transporter in cultured rat adipocytes." The Examiner admits that, "Al-Hasani did not teach the use of siRNA." The Examiner then states that "Clancy taught that the activity of a polypeptide in a cell can be controlled by several alternative means including the use of negative mutants of the protein and the use of antisense or siRNA directed at the mRNA encoding the protein." With respect to Paquereau, the Examiner alleges that "Paquereau taught a method of delivering nucleic acids to mammalian cells by electroporation using a potential of 0.15-0.2 kV and a capacitance of 960 micro F. These conditions minimized cell damage and increased cell survival." In conclusion, the Office Action states, on page 4, that, "it would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the electrical potential and capacitance used in the electroporation of the cells of Al-Hasani because it was recognized in the art that these variables could affect the amount of cell damage caused by electroporation, as well as cellular survival after electroporation."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to apply a flexible teaching, suggestion, or motivation test to combine known elements in order to show that the combination is obvious. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). Importantly, the *KSR* Court noted that "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (*In re Kahn*, 441 F.3d 911,988 (CA Fed. 2006) cited with approval in *KSR*).

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness since the skilled artisan would have found neither a reasonable expectation of success nor the motivation to arrive at the claimed invention given the teachings of the cited references.

The claims, as amended herein, are directed to a method of identifying a gene that affects glucose transport, or a method of identifying a gene involved in an insulin response disease or disorder, the methods comprising: (a) contacting ***a culture of isolated adipocytes*** with siRNA targeted against the gene, thereby forming a mixture; (b) electroporating the mixture ***under conditions such that the siRNA is introduced into the adipocytes at an efficiency such that expression of the targeted gene is reduced by at least 70% in the culture of adipocytes when maintained under conditions suitable for the siRNA to mediate RNAi of the targeted gene***; and (c) assaying glucose transport in the adipocytes, wherein a modulation in glucose transport indicates that the targeted gene affects glucose transport; thereby identifying a gene that affects glucose transport or a gene that is involved in an insulin response disease or disorder.

The claims have been amended to recite an essential feature of the instant invention which distinguishes the claimed invention over the cited art. As taught in the instant specification and described in detail in the arguments presented herein, in order to effectively identify target genes that affect glucose transport in adipocytes, ***it is essential that the adipocyte population exhibit sufficient reduction in expression of the targeted gene to be able to reliably assay that gene's effect on glucose transport***. The instant inventors achieved such an effect by developing a highly efficient methodology of introducing nucleic acid molecules which interfere with expression of the targeted gene, *i.e.*, siRNAs mediating RNA intererference of the targeted gene. The methodology efficiently introduces the siRNA into ***virtually all of the adipocytes in the population*** with little to no adverse toxicity effects. Moreover, the siRNAs are highly effective at reducing expression of the target gene after sufficient culturing of the population. Thus, the methodology provides for highly efficient introduction of the siRNAs such that gene reduction occurs at a level suitable to assay the gene's effect on the glucose transport activity of the adipocyte population. Such a methodology is nowhere taught or suggested by the prior art.

Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) describe the characterization of the mechanism of GLUT4 endocytosis by overexpressing a dominant-negative mutant of dynamin-1 in rat adipose cells (see page 17504, column 2, lines 46-48 of Al-

Hasani *et al.*). In order to study the role of dynamin in GLUT4 endocytosis, Al-Hasani *et al.* overexpress a plasmid encoding a dominant-negative mutant of dynamin-1 in isolated rat adipose cells. The effects of dynamin-1 on GLUT4 trafficking are monitored using a co-transfected recombinant GLUT4 containing a hemaglutinin (HA) tag. The methodology of Al-Hasani is designed to transfect adipose cells with ***DNA and DNA expression plasmids*** (see, *e.g.*, page 17505, column 1, second paragraph of Al-Hasani *et al.*). In particular, the methods involve transfection of cells with large amounts of ***plasmid DNA*** (*e.g.*, 5 μg plasmid DNA per transfection). Large amounts of carrier DNA are utilized (*e.g.*, 100μg carrier DNA). Pulse conditions are specified for the described ***plasmid DNA*** transfection. The reference is silent as to capacitance. Specifically, Al-Hasani *et al.* disclose that "***only 10% of the cells are transfected***" (see, *e.g.*, page 17505, right column, second paragraph of Al-Hasani *et al.*) (Emphasis added). It would not have been obvious, based on the teachings of Al-Hasani *et al.* regarding the low efficiency of DNA transfection into adipocytes that ***successful electroporation of an adipocyte population with siRNA such that gene reduction would occur at a level suitable to assay the gene's effect on the glucose transport activity of the adipocyte population could be accomplished***, as required by the currently pending claims.

Clancy *et al.* (US 20030087259) fail to remedy the deficiencies of Al-Hasani *et al.* Clancy *et al.* simply teach diagnostic assays for detecting bone and cartilage formation and therapeutic methods for treating disease and disorders related to bone and cartilage formation or resorption. Clancy *et al.* teach siRNAs as a component of a composition comprising "a plurality of antagonists of a plurality of genes" (see *e.g.*, para. [0009]). Clancy *et al.* also teach siRNAs as potential agents for "blocking or reducing the expression of a gene or the activity or level of the encoded polypeptide that is modulated, *e.g.*, upregulated, during normal bone or cartilage formation" (see *e.g.*, para. 0239)). There is no teaching or suggestion in Clancy *et al.* regarding the successful electroporation of an adipocyte population with siRNA such that gene reduction would occur at a level suitable to assay the gene's effect on the glucose transport activity of the entire adipocyte population.

The Paquereau reference does not teach or suggest the claimed invention either alone or in combination with the Al-Hasani and Clancy references. Paquereau describes the transfection of ***hepatocyte cells with DNA*** (see *e.g.*, page 148, column 2, lines 1-4 of Paquereau *et al.*). In particular, Paquereau describes the electroporation of high concentrations of isolated hepatocytes (*e.g.*, 16-20 x $10^6$ heaptocytes, *i.e.*, 20-25 x $10^6$ hepatocytes per 0.8 ml) with large amounts of

plasmid DNA (*e.g.*, 30 μg DNA per 0.8ml) in the presence of large amounts of carrier DNA (*e.g.*, 400 um). The transfection methods are optimized to obtain high levels of expression of the reporter gene CAT. As discussed previously, siRNAs and plasmid DNA are quite different chemical entities. Accordingly, one of skill in the art at the time of the instant invention would not have not had a reasonable expectation of success in utilizing certain of the parameters disclosed in Paquereau for transfection of large amounts of plasmid DNA to arrive at the siRNA electroporation methods featured in the claimed invention based upon this teaching, nor would one be motivated to combine these references. Moreover, there is nothing in Paquereau *et al.* which would motivate a skilled artisan to combine the teachings with those of Al-Hasani *et al.* and Clancy *et al.* to arrive at the claimed methods for identifying genes affecting glucose transport or genes involved in insulin-response diseases or disorders. Paquereau *et al.* relates to DNA transfection of hepatocytes to preserve a growth hormone response and is wholly unrelated to the art of glucose transport.

Moreover, Applicants respectfully submit that the ordinary artisan would not have been motivated to combine the teachings of the Al-Hasani *et al.* with those of Clancy *et al.* and Pacquereau *et al.* to arrive at Applicants claimed methodology. Even if the skilled artisan were to rely on Clancy *et al.* for teaching that siRNAs as an agent capable of blocking gene expression, he would not have been motivated to substitute the ***DNA plasmids*** transfected in Al-Hasani with such siRNAs. The mere fact that Clancy *et al.* lists siRNAs and dominant negative mutants as potential gene blocking compounds in a more extensive list of gene blocking compounds, *e.g.*, antisense molecules, ribozymes, triplexes, aptamers, does not rise to the level of a motivation to select one specific member from the recited antagonist list for use in the featured methodology. Moreover, there is nothing in Clancy *et al.* which would motivate a skilled artisan to combine the teachings with those of Al-Hasani *et al.* to arrive at the claimed methods for identifying genes affecting glucose transport or genes involved in insulin-response diseases or disorders. In particular, Clancy relates to diagnostic and therapeutic methods for detecting and/or treating bone and cartilage formation and is wholly unrelated to the art of glucose transport.

The Office Action has failed to point to any teaching in the cited references which would impel one of ordinary skill in the art to combine the teachings of the references in order to arrive

at the presently claimed invention. It is established law that "[w]hile the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying 'a ***reason*** that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (quoting *KSR,* 127 S. Ct. at 1731) (emphasis added). Although the prior art reference, or references when combined, need not teach or suggest all of the claim limitations, a *reason* must be given why the differences between the prior art and the claimed limitation would have been obvious to one of skill in the art (see Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103, Federal Register, Vol. 72, No. 195).

"A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of argument reliant upon ex post reasoning." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. at 1742. Accordingly, "[a] flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis." *In re Translogic Tech.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). However, it is of particular importance to detect evidence of nonobjective criteria showing nonobviousness beyond the *prima facie* analysis, including "unexpected results... skepticism of experts and copying – other respected sources of objective evidence of nonobviousness – as well as commercial success... this evidence is not just a cumulative or confirmatory part of the obviousness calculus but ***constitutes independent evidence of nonobviousness***." (Emphasis added). *Ortho-McNeil Pharmaceutical v. Mylan Labs* (Fed. Cir. 2008). The courts have also emphasized that, in retrospect, the inventor's "pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of the invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted." *Ortho-McNeil Pharmaceutical v. Mylan Labs* (Fed. Cir. 2008).

Unexpected Results and Skepticism of Experts

The instant application provides evidence of nonobjective criteria showing nonobviousness beyond the *prima facie* analysis, including unexpected results and skepticism of experts. For example, it was well known in the art at the time of filing that electroporation of DNA into adipocytes only leads to the successful expression of DNA in only a small minority of

the adipocyte population (***approximately 1-10%***[1]). In contrast, in order for siRNA to successfully silence the gene of interest, *i.e.,* mediate RNA interference, in the population of adipocytes, as currently claimed, it is required that virtually all of the cultured adipocytes (***approximately 100%***) take up functional siRNA. ***Since the successful electroporation of DNA into a population of adipocytes is typically less than 10% efficient, it would not have been obvious to one of ordinary skill in the art at the time of filing of the instant invention that electroporation of siRNA into a culture of isolated adipocytes would be nearly 100% efficient***[2] and that ***the adipocyte population would exhibit sufficient reduction in expression of the targeted gene***. A skilled artisan would have had an appreciation of these significant differences and would not have reasonably expected that substitution of the siRNAs of Clancy *et al.* for the plasmid DNAs transfected in Al-Hasani *et al.* would be successful.

As indicated by the court, in retrospect, the "pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of the invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted." *Ortho-McNeil Pharmaceutical v. Mylan Labs* (Fed. Cir. 2008). In the instant application, the previously filed declaration of the inventors under 37 CFR §1.132, attached herein as Appendix A, further supports the nonobviousness of the invention and the skepticism of experts at the time of filing of the application. The declaration establishes that, prior to Applicants' demonstration that such electroporation of siRNA into a culture of isolated adipocytes was possible according to the claimed methods of this invention, there was no reasonable expectation by one of ordinary skill in the art that such successful electroporation and sufficient reduction in expression of the targeted gene could be accomplished.

Appendices B and C further demonstrate the skepticism of one of ordinary skill in the art at arriving at the claimed invention. As demonstrated in Appendix B, Jain discloses that "***adipocytes are fully differentiated cells with no proliferation and are thus difficult to transfect*** by either RNAi or ASO approaches" (see, *e.g.,* page 308, middle column, first paragraph) (Emphasis added). As demonstrated in Appendix C, Venugopal *et al.* disclose that "***adipocytes... proved difficult to transfect efficiently with siRNA***" (see, *e.g.,* page 17122, second column, first full paragraph) (Emphasis added).

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[1] See, *e.g.,* page 40, lines 15-17 of the instant specification and page 17505, right column, second paragraph of Al-Hasani *et al.*

[2] Using labeled siRNA, Figure 1B, left panels, and Example 2, page 40, lines 1-17, of the specification demonstrate that the electroporation of siRNA into adipocytes was, unexpectedly, nearly 100% efficient.

Applicants, themselves, also describe in their specification the problems existing in the art at the time of the invention. In particular, Applicants teach in the specification on page 1, lines 23-24 that adipocyte "cells are difficult to work with and are not easily transfected with reagents that work in other cells such as fibroblasts." Furthermore, it was well known in the art at the time of the invention that the transfection of a culture of cells with DNA differs dramatically from the transfection of a culture of cells with siRNA, and that the transfection of siRNA varies greatly based on cell-type. For example, Walters and Jelinek[3] teach that the effectiveness of siRNAs may depend on the method of transfection (see title and abstract of Walters and Jelinek (2002) *Antisense and Nucleic Acid Drug Development* 12:411-418). More specifically, Walters and Jelinek teach the "striking dependence of dsRNA-mediated gene silencing in some cells on the methods of dsRNA transfection"(see Abstract of Walters and Jelinek). Additionally, Weil *et al.*[4] also teach that "the first difficulty with implementing RNA interference in a new cell type is optimizing the transfection procedure" (see page 1244, last paragraph of the Introduction, of Weil *et al.* (2002) *BioTechniques* 33:1244-1248).

These references indicate that, not only is the transfection of cells with siRNA different than transfection of cells with DNA, but siRNA transfection is complicated and the transfection procedure varies significantly from cell-type to cell-type. Thus, the instant application provides evidence of nonobjective criteria showing nonobviousness beyond the *prima facie* analysis, including unexpected results and skepticism of experts.

Copying and Commercial Success

The instant application further provides evidence of nonobjective criteria showing nonobviousness beyond the *prima facie* analysis, including copying and commercial success.

Robinson *et al.,* enclosed herein as Appendix F, is a post-filing reference from 2006 that demonstrates the difficulty of transfecting adipocytes with siRNA and the successful use of the present invention to electroporate adipocytes with siRNA. Robinson *et al.* state that "adipocytes are difficult to transfect, and until recently, successful siRNA transfection was achieved only via electroporation" (see, *e.g.,* page E885, second column, third full paragraph). Robinson *et al.* go on to cite a 2004 scientific publication of one of the inventors of the instant application, M.

[3] A copy of which is attached herein as Appendix D.
[4] A copy of which is attached herein as Appendix E.

Czech, ***as the first group which was successful in transfecting adipocytes with siRNA using electroporation***.

There is further evidence of copying and commercial success. As demonstrated in Appendix G, the commercially available Panomics DeliverX Plus siRNA Transfection Kit Brochure discloses that "[t]ransfection of siRNA into differentiated 3T3-L1 adipocytes... has only been accomplished by electroporation" (see, *e.g.,* first page, left column) and specifically references the 2003 *Proceedings of the National Academy of Sciences* scientific publication by the instant inventors which corresponds to the instant patent application. This Brochure goes on to further disclose that "***adipocytes... represent one of the most difficult-to-transfect cell lines used routinely in cell biology studies***" and that their product solves this difficult problem (see, *e.g.,* page 2, right column, second full paragraph) (Emphasis added).

Thus, the instant application provides evidence of nonobjective criteria showing nonobviousness beyond the *prima facie* analysis, including copying and commercial success. In summary, Applicants respectfully submit that the ordinarily skilled artisan at the time of Applicants' invention would not have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) in view of Clancy *et al.* (US 20030087259).

***Response to Non-Final Office Action***

In the Non-Final Office Action mailed on October 3, 2007, the Examiner alleges that "it was routine in the art at that time to optimize electroporation conditions... [and] the conditions of electroporation of mammalian cells were result effective variables that were obvious to optimize." Specifically, the Examiner is of the opinion that

> [t]o the extent that this is an argument of unexpected results, it is unpersuasive because the claims are not commensurate in scope with the results obtained... the assertion that, 'in order for siRNA to successfully silence the gene of interest, i.e., mediate RNA interference, as currently claimed, it is required that virtually all of the adipocytes... take up functional siRNA.' This assertion does not appear to be true. Al Hasani was capable of studying the effect on GLUT4 intracellular recycling by recombinant expression of GLUT4 and either GTPase dynamin or a GTPase-negative dynamin. Rat adipocytes were transfected with expression vectors encoding GLUT4 and either of the dynamins, and the effects on

> GLUT4 translocation in the presence of insulin were observed... Applicant has not explained why 100% transfection efficiency would be required when studying glucose transport using siRNA to downregulate a cellular process, when 10% efficiency (or far less) was sufficient for studying the same process by transfection of separate expression vectors encoding GLUT4 and dynamin... Applicant has presented no evidence that electroporation conditions used for [DNA] plasmids would not function for siRNAs. (Emphasis added).

Applicants respectfully traverse the Examiner's rejection. Applicants' invention is a novel methodology capable of silencing gene expression, *e.g.*, endogenous gene expression, in ***virtually every adipocyte in a population***. This key aspect of Applicants' invention is featured in the claims. Al-Hasani *et al.* overexpress HA-tagged GLUT4 such that approximately 10% of the population is transfected, and co-express either wild-type or mutant dynamin (efficiency unknown) in order to determine whether dynamin plays a role in GLUT4-mediated glucose transport. The mere fact that Al-Hasani *et al.* were able to inefficiently study glucose transport function in a population where only a small percentage of cells were transfected is irrelevant to the claimed invention. As compared to the inefficient, indirect methodology of Al-Hasani *et al.*, Applicants' claimed invention provides an unexpected, highly efficient methodology: a method of introducing siRNA into ***virtually all of the adipocytes (approximately 100%[5]) in the population*** in order to more efficiently reduce expression of a targeted gene. The fact that the inefficient, indirect methodology of Al-Hasani *et al.* was previously being utilized in the art further supports the nonobviousness of the improved, highly efficient methodology which is featured in the pending claims.

In view of the foregoing, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of Paquerequ *et al.* (Anal. Biochem. 204(1):147-151, 1992). Therefore, the claimed invention is not obvious in view of the cited art. Applicants

[5] Using labeled siRNA, Figure 1B, left panels, and Example 2, page 40, lines 1-17, of the specification demonstrate that the electroporation of siRNA into adipocytes was, unexpectedly, nearly 100% efficient.

respectfully request withdrawal of the rejection of the claims under 35 U.S.C. §103(a) and favorable reconsideration.

*Rejection of claim 49 under 35 U.S.C. § 103(a)*

The Examiner has rejected claim 49 as being unpatentable over Al-Hasani *et al.* and Clancy *et al.* and further in view of Standaert *et al.* (J. Biol. Chem. 272(48):30075-30082, 1997). The Examiner's comments with respect to Al-Hasani and Clancy are summarized above. The Examiner states that, "Standaert taught methods of studying the effect of a gene expression of protein kinase C zeta (PKC-zeta) on glucose transport." The Office Action summarizes that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to extend the studies of Al-Hasani to studies of glucose uptake."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

The currently pending claims are set forth as above. To briefly summarize, the amended claims are directed to a method of identifying a gene in adipocytes that affects glucose transport or a gene involved in an insulin response disease or disorder, and that it is essential to the method that electroporation of siRNA into a culture of adipocytes be ***efficient*** and that ***the adipocyte population exhibit sufficient reduction in expression of the targeted gene to be able to reliably assay that gene's effect on glucose transport***. The legal requirements to establish a *prima facie* case of obviousness are set forth above. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness since at the time the invention was made there was neither a reasonable expectation of success in making the claimed invention nor motivation to combine the references in the manner suggested by the Examiner. The teachings of Al-Hasani *et al.* and Clancy *et al.* are set forth above. As discussed previously, based on the teachings of the references, there was no reasonable expectation of success in making the claimed invention. Additionally, the Examiner has not provided the requisite motivation to combine these references.

The Standaert reference does not teach or suggest the claimed invention either alone or in combination with the Al-Hasani and Clancy references. Standaert, like Al-Hasani, is directed toward the study of insulin stimulation in glucose transport by transfection of ***rat adipocytes***

***with plasmid DNA*** (see *e.g.,* page 148, column 2, lines 1-4 of Standaert *et al.*). Like Al-Hasani, Standaert fails to rectify the deficiency of teaching of features necessary to electroporation of siRNAs as in the claimed invention. Applicants submit that one of skill in the art at the time of the instant invention would not have not had a reasonable expectation of success in making the claimed invention based upon this teaching, nor would one be motivated to combine these references.

In view of the foregoing, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.* (J. Bio. Chem. 273(28):17504-17510, 1998) and Clancy *et al.* (US 20030087259) and further in view of Standaert *et al.* (J. Biol. Chem. 272(48):30075-30082, 1997). Therefore, the claimed invention is not obvious in view of the cited art. Applicants respectfully request withdrawal of the rejection of claim 49 under 35 U.S.C. §103(a) and favorable reconsideration.

*Rejection of claims 52-55 under 35 U.S.C. § 103(a)*

The Examiner has rejected claims 52-55 as being unpatentable over Al-Hasani *et al.* and Clancy *et al.* and Paquereau *et al.* and further in view of McSwiggen *et al.* (US Patent 7,022,828). The Examiner states on page 7 of the Office Action that, "[t]he teachings of Al-Hasani, Clancy, and Paquereau... can be combined to render obvious methods of identifying a gene that affects glucose transport by assaying insulin-mediated GLUT4 translocation in the presence or absence of dynamin, wherein dynamin concentration is modulated through siRNA delivered by electroporation." Further, on page 7, the Office Action states that "McSwiggen taught methods of inhibiting gene expression using siRNA, and taught that the stability of siRNA molecules could be enhanced through the use of modified bases." In conclusion, the Office Action summarizes that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to use modified siRNA oligonucleotides in the invention of Al-Hasani as modified by Clancy and Paquereau... in order to enhance the function of the oligonucleotides, as taught by McSwiggen."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

The McSwiggen reference does not teach or suggest the claimed invention either alone or in combination with the Al-Hasani, Clancy, and Paquereau references. McSwiggen teaches modified siRNA oligonucleotides which modulate the expression or function of IKK genes, such as IKK-gamma, IKK-alpha, or IKK-beta, and PKR genes in several cell types. However, McSwiggen does disclose any details of transfecting ***adipocytes*** with siRNA. Thus, McSwiggen fails to rectify the deficiency of teaching of the Al-Hasani, Clancy, and Paquereau references. Moreover, there is nothing in McSwiggen which would motivate a skilled artisan to combine the teachings with those of Al-Hasani, Clancy, and Paquereau to arrive at the claimed methods for identifying genes affecting glucose transport or genes involved in insulin-response diseases or disorders. McSwiggen relates generically to the chemistry of siRNA derivatives and is wholly unrelated to the art of glucose transport.

In view of the foregoing, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention based on the teachings of Al-Hasani *et al.,* Clancy *et al.,* Paquereau *et al.* and further in view of McSwiggen *et al.* (US Patent 7,022,828). Therefore, the claimed invention is not obvious in view of the cited art. Applicants respectfully request withdrawal of the rejection of claims 52-55 under 35 U.S.C. §103(a) and favorable reconsideration.

## REMARKS

In view of the foregoing, entry of the amendments and remarks presented, favorable reconsideration and withdrawal of the rejections, and allowance of this application with the pending claims are respectfully requested. If a telephone conversation with the Applicant's attorney would expedite prosecution of the above-identified application, the Examiner is invited to call the undersigned at (617) 227-7400.

Dated: April 3, 2008

Respectfully submitted,

By _____

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